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Circulating leukocyte integrin expression in Wegener's granulomatosis.

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Leukocyte adhesion and infiltration are important in the pathogenesis of Wegener's granulomatosis (WG). We tested the hypothesis that the expression of the beta 1-chain integrin VLA-4 (CD49d/CD29) and the beta 2-chain integrins LFA-1 (CD11a/CD18), Mac-1 (CD11a/CD18), and gp150,95 (CD11c/CD18) is increased on leukocytes in patients with active WG. Fifteen patients with active WG as defined by positive antineutrophil cytoplasmic autoantibody (cANCA) titers and biopsy, 30 patients with WG in remission as defined by negative cANCA titers and/or immunosuppressive therapy, 25 normal control subjects, and 12 patients with other inflammatory renal and systemic diseases were studied. Surface expression of LFA-1, Mac-1, p150, 95, and VLA-4 on neutrophils, lymphocytes, and monocytes was measured by fluorescent antibody cell sorting with monoclonal antibodies against CD11a, CD11b, CD11c, CD18, CD49d, and CD29 respectively. Immunocytochemistry and confocal microscopy were also utilized. beta 1 (CD29) and beta 2 (CD18) integrin subunit expression on neutrophils, monocytes, and lymphocytes from patients with acute WG was significantly increased compared with healthy persons and compared with patients with treated vasculitis. Furthermore, the alpha-integrin subunit CD11b expression was increased on granulocytes and monocytes, but not on lymphocytes. Finally, the alpha-integrin subunit CD11a expression was increased on monocytes. Immunocytochemistry showed that the increased immunoreactivity on neutrophils was evenly distributed on the plasma membrane and in the cytosol. Immunosuppression resulted in decreased expression of the beta 1 and beta 2-integrin subunits. It was concluded that the integrin adhesion molecules, particularly Mac-1 (CD11b/CD18), are upregulated on leukocytes in active WG. This finding suggests a role for integrin expression in the pathogenesis of WG and a possible clue for treatment.

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Polymorphonuclear leucocyte migration through human dermal fibroblast monolayers is dependent on both beta 2-integrin (CD11/CD18) and beta 1-integrin (CD29) mechanisms.

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Accumulation of leucocytes in inflammation involves their migration through vascular endothelium and then in the connective tissue. We investigated human polymorphonuclear leucocyte (PMNL) migration through a biological barrier of human dermal fibroblasts grown on microporous filters, as a model of PMNL migration in the connective tissue. PMNL did not migrate through a fibroblast monolayer unless a chemotactic factor, e.g. C5a, interleukin-8 (IL-8) or zymosan-activated plasma (ZAP; C5adesArg), was added. This migration was partially inhibited (35-70%, depending on the stimulus) by treatment of PMNL with monoclonal antibody (mAb) to CD18 (beta 2-integrins). Most of the CD18-independent migration was inhibited by mAb to beta 1-integrins (CD29). Inhibition by mAb to beta 1 was observed when the PMNL, but not the fibroblasts, were treated with mAb. The role of beta 1-integrins in PMNL transfibroblast migration was detectable only when the function of the CD11-CD18 complex was blocked, because mAb to beta 1-integrin alone had no significant effect on PMNL migration. Migration induced by C5a was more CD18-independent compared to IL-8 or C5adesArg. The CD18-independent migration was also inhibited by mAb to the beta 1-integrin subunits alpha 5 (of very late antigens-5; VLA-5) and alpha 6 (of VLA-6). Treatment of the fibroblasts (4 hr) with tumour necrosis factor-alpha (TNF-alpha) or IL-1 alpha enhanced C5a-induced PMNL transfibroblast migration and increased the proportion of migration utilizing the CD11-CD18 mechanism. However, TNF-alpha treatment had no effect on the degree of beta 1-integrin-dependent migration. These findings suggest that in response to the chemotactic factors C5a, IL-8 and C5adesArg, PMNL migration in the connective tissue is mediated by both CD11-CD18 (beta 2) and beta 1-integrins on the PMNL. The VLA-5 and VLA-6 members of beta 1-integrins are involved in this process. This is in contrast to PMNL migration across endothelium in this system, which is virtually all CD18 dependent with no significant role for beta 1-integrins.

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